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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,178	01/11/2002	Noriyuki Kasahara	06666-022002	7589

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/045,178	KASAHARA ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,41-46,49-51,56,59,61,63-73,75,77-82 and 87* is/are pending in the application.

4a) Of the above claim(s) *46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,41-45,49-51,56,59,61,63-73,75,77-82 and 87* is/are rejected.

7)☒ Claim(s) *51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/26/2007 has been entered.

2. Claims 1-40, 47, 48, 52-55, 57, 60, 62, 74, 76, and 83-86 have been cancelled. Claim 46 has been withdrawn. Claims 41, 66, 80, and 82 have been amended. Claims 87-96 are new.

Claims 41-45, 49-51, 56, 59, 61, 63-73, 75, 77-82, and 87-96 are pending and under examination.

3. The rejection of claims 41-45, 49-51, 56, 58, 59, 61, 63-65, 80 and 81 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 20 of U.S. Patent No. 6,899, 871 is withdrawn because Applicant submitted a terminal disclaimer on 01/26/2007.

The rejection of claims 66-73, 75, 77-79 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 and 21 of

U.S. Patent No. 6,899, 871 is withdrawn because Applicant submitted a terminal disclaimer on 01/26/2007.

The rejection of claim 82 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19 of U.S. Patent No. 6,899, 871 is withdrawn because Applicant submitted a terminal disclaimer on 01/26/2007.

The rejection of claims 41-45, 49-51, 56, 58, 59, 61, 63-73, 75, and 77-82 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in response to Applicant's arguments filed 01/26/2007.

New Rejections

Claim Objections

4. Claim 51 is objected to under 37 CFR 1.75(c) as being in improper form because it is dependent from the subsequent claim 64.

Claim Rejections - 35 USC § 112, 2nd paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

6. Claims 41, 58, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the recitation of "wherein the tissue specific promoter sequence is associated with probasin or a growth regulatory gene" can be interpreted as either (i) the tissue specfic promoter is operably linked to

probasin or the growth regulatory gene and drives their expression, or (ii) the tissue specific promoter is the probasin promoter or a growth regulatory gene promoter. Since the metes and bounds of the claims cannot be determined, the claims are indefinite.

Claim Rejections - 35 USC § 112, enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 41-44, 49-5156, 58, 59, 61, 63-73, 75, 77-82, and 87-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a subject having a cell proliferative disorder by local or topical (when treatment of proliferative conditions of the skin is desired) administration of a replication competent retrovirus, does not reasonably provide enablement for a method of treating a subject having a cell proliferative disorder by systemic administration of a replication competent retrovirus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or

guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

While the both the art and the specification teach successful local (i.e., intratumor) delivery of retrovirus, neither neither the art nor the specification teach other efficient means of retroviral delivery for therapy. It is noted that the art teaches that delivery of virally expressed genes other than intratumor injection (i.e., intravascular or intracavitary injections) presents barriers to the delivery of the target genes to the tumor cells. For example, Meng et al. (Gene Therapy of Cancer, Chapter 1, 1999, pp. 3-20, p. 6, column 1; of record) teach:

> "In intravascular administration, instillation into a peripheral vein dilutes the vehicle, so only a small portion may ultimately reach the tumor. Intravascular administration also elicits a powerful immune response. Tropism for organs such as the liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous if the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass. In the case of intracavitary administration (i.e., intrapleural or intraperitoneal), the surface of the tumor mass is coated by virus, but intratumoral delivery within a solid mass represents an important barrier"

Given these teachings and the lack of guidance in the specification, one of skill in the art would not reasonably predict that routes of delivery other than intratumor delivery would result in successful therapy. Therefore, the specification provides enough support for a method of treating a subject having a cell proliferative disorder by local or

topical (when treatment of proliferative conditions of the skin is desired) administration of a replication competent retrovirus.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 41-45, 49-51, 56, 61, 66, 70, 71, 73, 75, 77-80, 87, 89, and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. (Cancer Research, 1993, 53: 83-88), in view of both Martuza (Nature Medicine, 1997, 3: 1323) and Martuza et al. (U.S. patent No. 5,585,096).

** It is noted that murine leukemia virus (MLV) is not a species but rather a genus comprising several species among which is Moloney murine leukemia virus (MoMLV). The claims reciting MLV are interpreted as being drawn to MoMLV because Applicant did not specifically identified the MLV species.

Ram et al. teach a method of treating glioblastoma in rats by *in vivo* intratumoral administration to the rats of a therapeutically effective amount of cells producing a retrovirus comprising 5' and 3' long terminal repeats (LTR) and a heterologous nucleic acid sequence encoding for the HSV thymidine kinase (tk) (i.e., a suicide gene) that uses the 5' LTR as its promoter (i.e., operably linked to a regulatory nucleic acid sequence), and contacting the rats with ganciclovir (i.e., a prodrug), wherein the

ganciclovir is activated by the tk expression of (claims 41, 42, 44, 45, 61, 66, 75, 77-79, 87, and 89) (Abstract, p. 83, columns 1 and 2, p. 84, column 1, p. 85, column 2). Ram et al. teach that the retroviral vector is Moloney murine leukemia virus or MoMLV, i.e., a murine leukemia virus or MLV (claims 49, 70, 71, 80, and 91) (p. 83, column 1). Ram et al. teach their approach as suitable for the treatment of localized tumors in humans (claims 43 and 56) (Abstract, p. 83, column 2, second full paragraph, p. 88, column 1). Ram et al. do not teach administering a replication competent retrovirus. Martuza (Nature Medicine) teaches that, although implanting producer cells into the brain is feasible, the method is not applicable to the treatment of glioblastoma in human because the producer cells are large and not motile and, because the vector cannot replicate, gene transfer occurs within a few cell-distances from the producer cells, which leads to inefficient gene delivery and suggests the use of replicating viral vectors (p. 1323, column 1, third paragraph, column 2, second full paragraph). Additionally, Martuza et al. (U.S. patent No. 5,585,096) teach replication deficient viral vectors as unsuitable for treating human tumors because of their inability to completely penetrate into tumors *in vivo*, wherein each replication defective retroviral particle can only enter a single cell and therefore it cannot productively infect other cells (column 1 bridging column 2). Martuza et al. teach that replication competent viral vectors are needed for efficient therapy, wherein the replication competent viral vectors are able to enter into tumor cells, make copies, lyse the cell and spread to the neighboring tumor cells (column 5, lines 14-18). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al. by using a replication

competent MoMLV (i.e., a retrovirus comprising GAG, POL, envelope, cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration into a target cell, wherein the GAG, POL, and envelope are the MoMLV GAG, POL, and envelope, as recited in claims 51, 70, 73, 80, and 91), with a reasonable expectation of success. The motivation to do so is provided by Martuza and Martuza et al., who teach the necessity to replace replication deficient viruses with replication competent viruses for efficient gene therapy in animals and humans. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches the successful use of replication competent viruses for cancer treatment. With respect to the limitation of the MoMLV being an amphotropic MoMLV (claims 50 and 71), absent evidence to the contrary, the MoMLV of Ram et al. is amphotropic. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

11. Claims 41-45, 49-51, 56, 58, 59, 61, 66, 70, 71, 73, 75, 77-80, 87-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with Martuza and Martuza et al., in further view of both Kuryama et al. (Int J Cancer, 1997, 71: 470-475) and Yan et al. (Prostrate, 1997, 32: 129-139).

** The rejection of claims 41, 58, and 59 is based on the interpretation that the claims recite probasin promoter or a growth regulatory gene promoter.

The teachings of Ram et al. taken with Martuza and Martuza et al. are applied as above for claims 41-45, 49-51, 56, 61, 66, 70, 71, 73, 75, 77-80, 87, 89, and 91. Ram et al. taken with Martuza and Martuza et al. do not teach a tissue-specific promoter

(claims 58, 88, 90, and 92), wherein the tissue specific promoter is the probasin promoter (claim 59). Kuryama et al. teach efficient antitumor effect by expressing tk under the control of the liver-specific albumin promoter (Abstract, p. 470, column 2, last paragraph, p. 471, column 1, first and second paragraphs, p. 472, column 1). Kuryama et al. do not teach the probasin promoter. Yan et al. teach targeted gene expression in the prostrate by using the probasin promoter (Abstract, p. 130, columns 1 and 2, p. 133, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al., Martuza, and Martuza et al. by using the probasin promoter of Yan et al., with a reasonable expectation of success. The motivation to use a tissue specific promoter is provided by Kuryama et al., who teach that by doing so, the efficiency of the antitumor effect is increased (Abstract, p. 471, column 1, first paragraph, p. 474, column 1, first full paragraph). One of skill in the art would have been motivated to use the probasin promoter to specifically target the suicide genes to prostrate tumors for increased treatment efficiency of such tumors. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches the successful use of tissue-specific promoters for targeted delivery of suicide genes to specific target sites. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

12. Claims 41-45, 49-51, 56, 61, 63-70, 71-73, 75, 77-80, 81, 82, 87, 89-91, 93, and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken

with Martuza and Martuza et al., in further view of Kasahara et al. (Science, 1994, 266: 1373-1376).

The teachings of Ram et al. taken with Martuza and Martuza et al. are applied as above for claims 41-45, 49-51, 56, 61, 66, 70, 71, 73, 75, 77-80, 87, 89-91. Ram et al. taken with Martuza and Martuza et al. do not teach a chimeric envelope, wherein the chimeric protein comprises a targeting ligand such as a receptor ligand (claims 63-65, 67-69, 81, 82, 93, and 95) or an ecotropic envelope (claim 72). Kasahara et al. teach tissue specific targeting of MoMLV retroviral vectors to cells expressing the erythropoietin (EPO) receptor by engineering the vector to encode a chimeric ecotropic MoMLV protein, wherein the chimeric envelope protein comprises EPO (p. 1373, column 2, p. 1374, column 3 bridging p.1375). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al., Martuza, and Martuza et al. by engineering their vector to encode for an ecotropic envelope fused to a receptor ligand, with a reasonable expectation of success. The motivation to do so is provided by Kasahara et al., who teach that such viruses can be used to specifically infect human cells expressing the ligand receptor and that such a strategy can be used for the treatment of cancer (p. 1373, column 1, p. 1375, column 1 bridging column 2, and column 3). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that such engineered retroviruses can be successfully made and used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

13. Claims 41-45, 49-51, 56, 61, 63-70, 71-73, 75, 77-80, 81, 82, 87, 89-91, and 93-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with Martuza, Martuza et al., and Kasahara et al., in further view of Kuryama et al.

The teachings of Ram et al. taken with Martuza, Martuza et al., and Kasahara et al. are applied as above for claims 41-45, 49-51, 56, 61, 63-70, 71-73, 75, 77-80, 81, 82, 87, 89-91, 93. Ram et al. taken with Martuza, Martuza et al., and Kasahara et al. do not teach a tissue specific promoter (claims 94 and 96). Kuryama et al. teach efficient antitumor effect by expressing tk under the control of the liver-specific albumin promoter (Abstract, p. 470, column 2, last paragraph, p. 471, column 1, first and second paragraphs, p. 472, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al., Martuza, Martuza et al., and Kasahara et al. by using a tissue specific promoter, such as the promoter of Kuryama et al., with a reasonable expectation of success. The motivation to use a tissue specific promoter is provided by Kuryama et al., who teach that by doing so, the efficiency of the antitumor effect is increased (Abstract, p. 471, column 1, first paragraph, p. 474, column 1, first full paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches the successful use of tissue-specific promoters for targeted delivery of suicide genes to specific target sites. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

14. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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